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Moxalactam Kinetics during Continuous Ambulatory Peritoneal Dialysis after Intraperitoneal Administration

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Moxalactam kinetics during continuous ambulatory peritoneal dialysis (CAPD) was followed in eight patients after a single intraperitoneal dose of 1 g. Approximately 60% of the dose was absorbed after a dwell time of 4 h. Dialysis solutions were exchanged at 4-h intervals with an overnight dwell of 8 h. The mean (± standard deviation) elimination half-life was 13.2 ± 2.9 h, and the mean apparent volume of distribution was 0.22 ± 0.08 liters/kg. Mean total clearance was 11.5 ± 2.4 ml/min, with a mean dialysis clearance of 2.3 ± 0.5 ml/min. The maximum concentration in plasma ranged from 24.5 to 54.1 μg/ml. Moxalactam concentrations in the peritoneal dialysis fluid were above 80 μg/ml during the first exchange and above 2 μg/ml for a further three exchanges. A suggested intraperitoneal dose regimen for patients undergoing CAPD is 1 g initially, followed by 15 to 25% of the recommended dose for normal patients given at the same time intervals, or 30 to 50% of the recommended dose at twice the usual intervals. Moxalactam is suggested for initial treatment of peritonitis in CAPD patients who do not have ready access to the antibiotic of choice.

Continuous ambulatory peritoneal dialysis (CAPD) is an increasingly popular form of dialysis treatment for end-stage renal disease. The major complication of this dialysis method is the frequency of episodes of peritonitis. These infective episodes are usually caused by gram-positive staphylococci, but other organisms, including gram-negative bacteria and fungi, have been implicated (22).

Many CAPD patients live in remote areas where access to trained personnel and new antibiotics is limited. The delays involved in travelling to the major dialysis centers may result in a worsening of the patient's condition and a longer hospital stay. Microbiological examination of the contaminated dialysate is necessary before antibiotic therapy directed against the infecting organism can be instituted, whereas empirical antibiotic therapy is instituted at the earliest opportunity after arrival at the dialysis center. Moxalactam has a useful spectrum of activity for this empirical treatment but requires trained personnel for administration via the recommended routes (intravenous or intramuscular).

Moxalactam is a semisynthetic β-lactam antibiotic with activity against a broad range of gram-positive and gram-negative aerobic and anaerobic bacteria (8, 21). In normal subjects, approximately 80% of an intravenous dose is excreted unchanged in the urine (11, 18), and it has been shown that patients with renal impairment require a change in the dose regimen to avoid drug accumulation (3, 12, 24). After the hemodialysis of patients with renal failure, an adjustment of the subsequent dose is necessary to compensate for the increased clearance of moxalactam during the dialysis period (2, 9, 12). However, for patients with renal failure, who are undergoing CAPD, dosage adjustment to account for any loss of moxalactam via the peritoneal cavity appears unnecessary (19, 24). No data are currently available on the pharmacokinetics of moxalactam after single-dose intraperitoneal administration. This study was performed to assess the concentration of moxalactam achieved in plasma and dialysis fluid after administration of a 1-g intraperitoneal dose to patients on CAPD and to compare the pharmacokinetic data obtained with previously reported results after intravenous administration to CAPD patients.

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MATERIALS AND METHODS

Subjects. Eight patients (six female, two male) suffering from end-stage renal disease, undergoing CAPD, and with no visible symptoms of peritonitis participated in the study (Table 1).

Subjects were given moxalactam disodium (equivalent to 1 g of moxalactam; Eli Lilly & Co.) in 2 liters of peritoneal dialysis fluid containing 0.5 to 4.25% anhydrous glucose (Travenol Laboratories, Australia) and 1,000 U of heparin. The solution was administered via a Tenckhoff catheter over a period of 10 ± 2 min (mean ± standard deviation) and allowed to remain for approximately 4 h. Further moxalactam-free dialysate exchanges were performed at intervals of approximately 4 h, with the exception of an overnight dwell time of approximately 8 h.

Sampling. During the initial dialysis exchange, plasma samples were obtained before and at 5, 10, 15, 20, and 30 min and 1, 2, and 4 h after the midpoint of drug administration. Subsequent plasma samples were obtained before drainage of successive dialysis solutions for a minimum of five exchanges. Dialysis fluid samples were obtained before and at 1, 2, and 3 h after administration and after drainage of the initial dialysis solution containing moxalactam. The next one or, where possible, two exchanges were similarly sampled immediately and at 1, 2, and 3 h after installation and after drainage. For each subsequent exchange, samples were taken after drainage.

Dialysis fluid samples were taken via the Tenckhoff catheter after allowing approximately 100 ml to drain. The drained fluid was restored to the peritoneal cavity. Any urine passed during the study was collected. Samples were stored at −20°C for a maximum of 40 days before the assay.

Assay. To 0.5 ml of plasma was added 0.1 ml of an aqueous solution of oxypurinol (150 μg/ml), 0.1 ml of hydrochloric acid, and 2.0 ml of ethyl acetate. The mixture was shaken on a vortex mixer for 15 s and centrifuged for 10 min. The upper

TABLE 1. Subject characteristics and drug history

Patient no.	Sex	Age (yrs)	Body wt (kg)	Period on CAPD	Comments[a]	Other drugs[b]
1	M	52	70	14 mo		Ranitidine, amoxicillin, Calcitriol
2	M	29	70	2 mo	On hemodialysis also, but not during test period.	Indomethacin, calcitriol
3	F	53	54	5 days		
4	F	65	67	14 mo		
5	F	73	48	6 wk		Calcitriol, cephalothin
6	F	61	60	1 mo	Myocardial infarction 3 wks before study. γGT, 251.	Digoxin, prazosin, prednisolone
7	F	53	45	2 wk	AST, 415. Liver function tests normal before and after admission.	Thyroxine, flunitrazepam, insulin
8	F	54	51	5 days	AST, 71; γGT, 135. Chronically abnormal liver function tests before study. Normal biopsy. Cholecystectomy.	Calcitriol, KCl, propranolol, nitrazepam, prednisolone, vancomycin

[a] γGT, Gamma glutamyltransferase in serum (normal, <35 U/liter); AST, asparatate aminotransferase in serum (normal, <45 U/liter). Liver function tests for bilirubin, gamma glutamyl transferase, and aspartate aminotransferase were normal except where specified.
[b] All patients were taking vitamins B and C and aluminium hydroxide.

organic layer was transferred to a pointed centrifuge tube, and the volume was reduced to approximately 0.1 ml under a gentle stream of nitrogen. After the addition of 0.05 ml of Tris buffer (0.2 mol/liter, pH 8.5), the mixture was shaken for 1 min and then centrifuged for 5 min. The ethyl acetate was aspirated, and 0.02 ml of the remaining aqueous phase was injected into the liquid chromatograph. Dialysis fluid samples subsequent to the first exchange were similarly assayed. For some patients it was necessary to extract the plasma and dialysis fluid samples after the addition of hydrochloric acid with either diethyl ether or chloroform before subsequent extraction with ethyl acetate. This removed any compounds with retention times similar to those of oxypurinol or the moxalactam epimers.

After the addition of 2 ml of a solution of oxypurinol (150 μg/ml), samples (2 ml) of dialysis solution from the initial exchange were diluted to 20 ml with distilled water. A 0.02-ml sample was injected into the liquid chromatograph.

Moxalactam containing equal proportions of the R- and S-epimers was used as a standard. Standard curves for both the R- and the S-epimer were prepared in either drug-free plasma or drug-free dialysis fluid by plotting the ratio of the peak height of each epimer to that of oxypurinol against the total moxalactam concentration. For the patient samples in which no interference with either epimer peak occurred, the total moxalactam concentration was calculated from both standard curves, and the two values were averaged. On the few occasions in which interference to one of the epimers occurred, the total concentration of moxalactam was determined from the peak height ratio of the other epimer (see below). For the determination of moxalactam in plasma, the coefficient of variation at 5 μg/ml was 5% (n = 10), and the limit of sensitivity was 1 μg/ml.

Chromatography was performed with an M-45 pump U6K injector, Radial Compression Module and A440 detector set at 280 nm (Waters Associates). The mobile phase (5% methanol in 0.05 mol of ammonium acetate buffer, pH 6.5, per liter) was pumped at 2.0 ml/min through a 10 μRadial-Pak C_{18} cartridge. The retention times for oxypurinol and R- and S- moxalactam were 4.7, 5.9, and 8.4 min, respectively (Fig. 1).

Data analysis. The elimination rate constant was determined by linear regression analysis of data for the log of the moxalactam concentration in plasma versus time from the time of drainage of the initial dialysis solution (i.e., in the postabsorption phase). The area under the plasma concentration-time curve was obtained by the trapezoid rule extrapolated to infinity with the elimination rate constant. The amount of drug absorbed was calculated by subtracting the amount remaining in the initial dialysis exchange solution after drainage from the amount added to the solution before administration. The amount absorbed was divided by the administered dose to determine the fraction of the dose absorbed.

The plasma clearance (CL_P) was calculated by dividing the amount absorbed by the area under the plasma concentration-time curve. Peritoneal dialysis clearance (CL_D) was calculated from each dialysis exchange, other than the initial exchange, by dividing the rate of recovery of moxalactam in the dialysate by the interpolated concentration in plasma at the midpoint of the respective dialysis interval; the values were averaged from each patient. The volume of distribution (V) was calculated by dividing the CL_P by the elimination rate constant. Unless otherwise indicated, data for the group are expressed as mean ± standard deviation.

RESULTS

Figure 2 shows the moxalactam concentrations achieved in both plasma and dialysis fluid for a typical patient. A log-linear relationship was observed between plasma concentration and time, after the initial dialysis exchange, for all patients ($r > 0.96$).

Figure 3 shows the average plasma concentration-time data for seven of the eight patients studied. The calculated half-life was 13.2 ± 2.9 h. Patient 8 was excluded because the concentration of moxalactam in plasma declined more slowly, with a half-life of 37.9 h (see below). Maximum concentrations in plasma, achieved at the end of the first dialysis exchange, ranged from 24.5 to 54.1 μg/ml (mean, 38.6 ± 12.7 μg/ml).

The concentration of moxalactam in the dialysis fluid at the end of the first dialysis exchange ranged from 84 to 286 μg/ml (mean, 214 ± 62 μg/ml). The concentration of moxalactam achieved in dialysis fluid at the end of three dialysis exchanges subsequent to the first exchange are shown in Fig. 4. Average concentrations of 15.6 ± 6.1, 8.4 ± 3.9, and 7.1 ± 4.1 μg/ml were found after the second, third, and fourth exchanges, respectively.

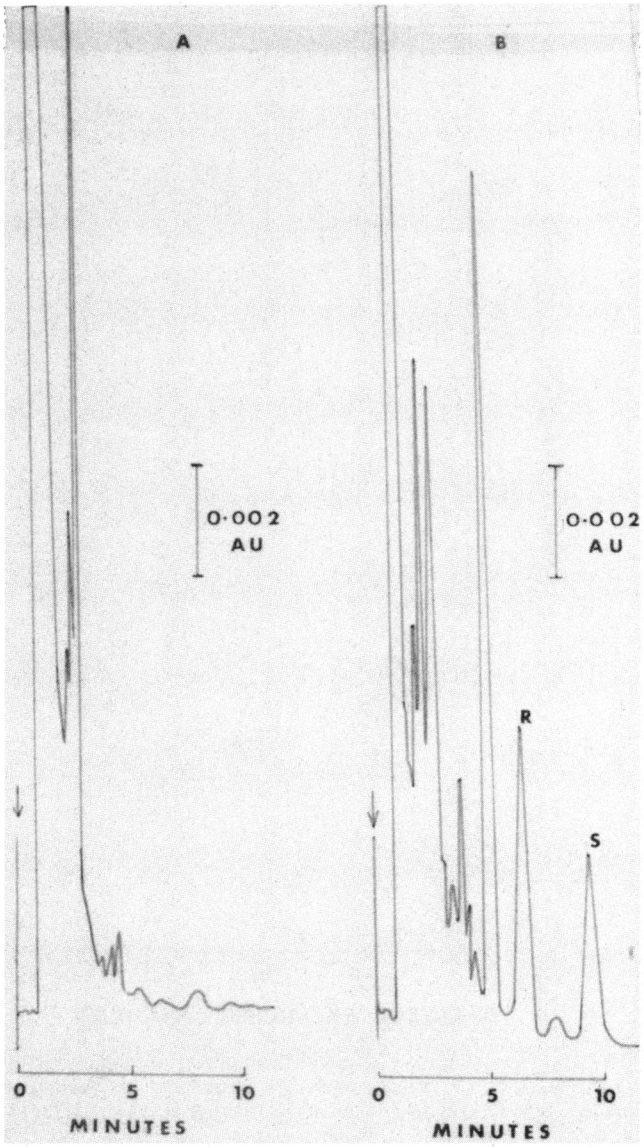

FIG. 1. Liquid chromatograms obtained after the extraction of blank patient plasma (A) and the same patient's plasma containing 9.1 μg of total moxalactam per ml (B).

The pharmacokinetic parameters are listed in Table 2. The values for patient 8 were excluded from the calculation of mean values for the various parameters. CL_D for each patient was calculated as the average (± standard deviation) of the clearance values found for each dialysis exchange subsequent to the initial exchange. However, for patient 7, only the second dialysis exchange was used to determine CL_D. Subsequent exchanges gave concentrations of moxalactam in the dialysis fluid which were too low to allow an accurate determination of clearance. Since the number of CL_D determinations for each patient differed, individual mean CL_D was used to calculate an average (± standard deviation) CL_D for the study group (excluding patient 8) of 2.3 ± 0.5 ml/min. CL_D accounted for 20.0 ± 5.2% of the total clearance in seven of the eight patients. For patient 8, CL_D accounted for 89.3% of the total clearance.

Only two of the subjects, patients 3 and 7, passed urine during the study. However, some of the urine samples were stored incorrectly after collection. Despite the fact that neither moxalactam epimer was detected in any of the urine samples that were stored correctly, these results were excluded from further analysis.

DISCUSSION

Moxalactam injection consists of approximately equal amounts of an R- and S-epimer. Yamada et al. (25), Lüthy et al. (13), and Wright et al. (24) reported that the half-lives of the R- and S-epimers in plasma differed after the intravenous administration of 1 g to normal subjects. It appears that, because it is less bound to plasma protein than the S-epimer (25), the R-epimer is more rapidly cleared by the renal route. This is reflected by a change in the ratio of the R-epimer to the S-epimer in plasma and urine with time (11, 13).

The above workers used a high-pressure liquid chromatography procedure which allowed the determination of the moxalactam epimers in plasma and urine without epimerization. Lüthy et al. (13) and Wright et al. (24) precipitated plasma proteins before high-pressure liquid chromatography. Preliminary experiments in this laboratory in which protein precipitation was used before high-pressure liquid

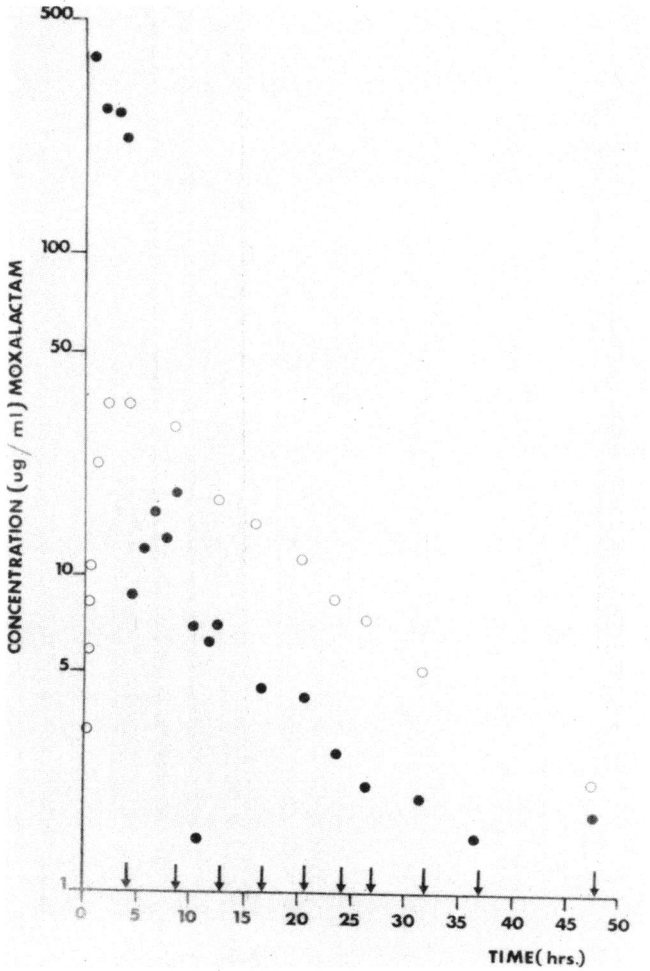

FIG. 2. Concentration-time curve of moxalactam in plasma (○) and dialysis fluid (●) after intraperitoneal administration of 1 g to patient 5. Arrows indicate the time at which dialysis fluid was exchanged.

chromatography for the determination of moxalactam in plasma from patients with renal failure showed a high level of interference from endogenous and exogenous compounds. Ziemniak et al. (26) also found that this procedure had limited application when plasma from critically ill patients with varying degrees of renal function was to be assayed for moxalactam. An improved method developed by these workers, in which solvent extraction was used after the addition of acid, was modified for use in this study. The modified procedure, however, allowed an interconversion to occur between the R- and S-epimers (7). Hence, the observed concentrations of the R- and S-epimers in plasma and dialysis fluid represent an artifact of the procedure. The ratio of the peak heights of the R-epimer to those of the S-epimer was the same in plasma and dialysis fluid for both the standard concentrations of total moxalactam and the patient samples. If any chromatographic interference did arise with either epimer, then the peak height of the other epimer could be used to determine the total moxalactam concentration. For patients with renal failure showing a long half-life for moxalactam, this assay procedure is acceptable, since the reported change in the ratio of the plasma concentrations of the R-epimer to those of the S-epimer with time is very small (24).

In the present study, for the six subjects who did not pass urine, moxalactam was cleared by either dialysis or other, nonrenal mechanisms. Presumably, most of the nondialysis (or other, nonrenal) elimination could be accounted for by hepatic clearance, since relatively high concentrations of moxalactam have been found in bile (14, 15). The calculated nondialysis clearance for five of these six subjects (excluding patient 8; see below) of 9.7 ± 2.4 ml/min compares favorably with that calculated by Aronoff et al. (2) (12.8 ± 2.0 ml/min), Jacobsen et al. (9) (9.3 ± 4.9 ml/min), and Singlas et al. (19) (4.2 ± 0.6 ml/min) after intravenous administration to subjects with a creatinine clearance of less than 8 ml/min. Jacobsen et al. (9) and Aronoff et al. (2) determined the concentration of moxalactam in plasma by microbiological assays, using *Escherichia coli* ATCC 10536 and *E. coli* ATCC 4157, respectively, as the test organisms. The susceptibility of either of the two microorganisms to each moxalactam epimer has not been reported. However, since no significant change with time in the ratio of the two epimers would be expected in patients with end-stage renal disease or with creatinine clearance values of less than 8 ml/min, then comparable results should be obtained irrespective of whether moxalactam is determined by high-pressure liquid chromatography or by microbiological assay.

The total CL_P determined in the subjects during the

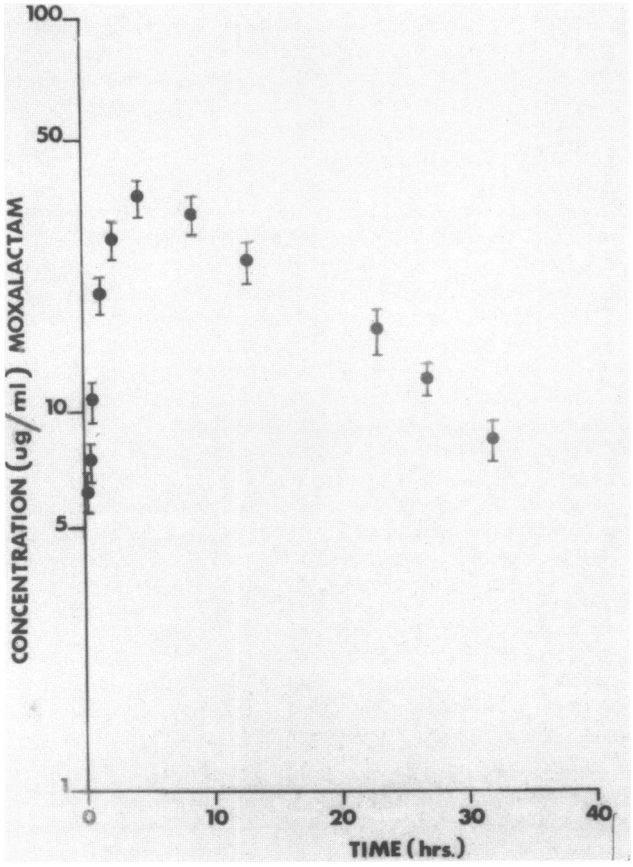

FIG. 3. Mean plasma concentration-time curve of moxalactam in seven patients after intraperitoneal administration of 1 g of moxalactam (mean ± standard error). Data for patient 8 was excluded.

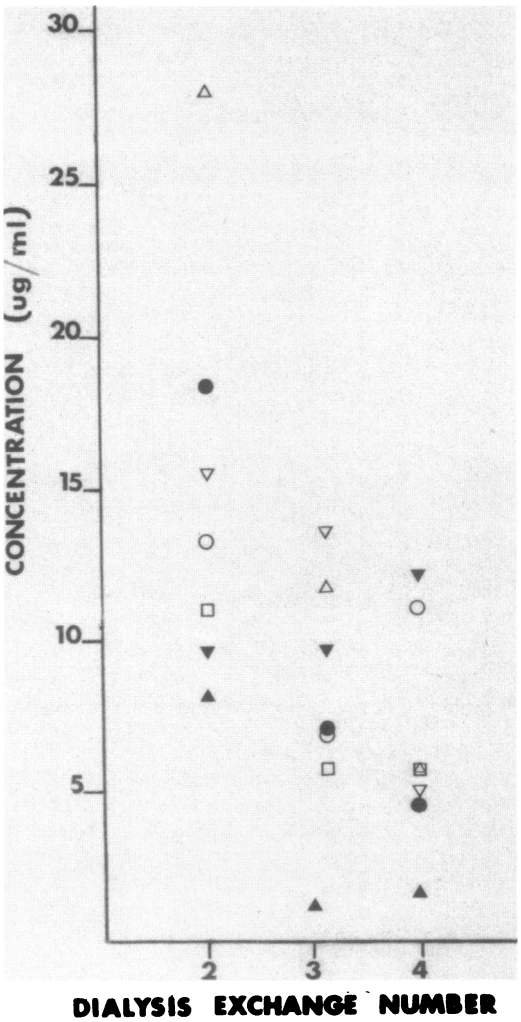

FIG. 4. Concentration of moxalactam in peritoneal dialysis fluid at the end of each dialysis exchange subsequent to the first exchange. Symbols represent patients as follows: ○, 1; ▽, 2; □, 3; △, 4; ●, 5; ▼, 6; ▲, 7.

TABLE 2. Moxalactam kinetics after intraperitoneal administration of 1 g

Patient no.	F^a	CL_P (ml/min)	CL_D (ml/min)	$k_{el}{}^b$ (h^{-1})	$t_{1/2}{}^c$ (h)	V (liters/kg)
1	0.51	9.2	2.8 ± 0.8	0.0394	17.6	0.20
2	0.63	9.7	1.7 ± 0.5	0.0550	12.6	0.15
3	0.62	8.7	1.8 ± 0.5	0.0592	11.7	0.16
4	0.47	13.7	2.8 ± 0.6	0.0606	11.4	0.20
5	0.56	14.8	2.8 ± 0.6	0.0643	10.8	0.29
6	0.83	12.9	1.7 ± 0.6	0.0624	11.1	0.21
7	0.43	11.6	2.2[d]	0.0408	17.0	0.40
8[e]	0.43	2.8	2.5 ± 1.0	0.0183	37.9	0.18
Mean ± SD	0.58 ± 0.13	11.5 ± 2.4	2.3 ± 0.5	0.0545 ± 0.0103	13.2 ± 2.9	0.22 ± 0.08

[a] Fraction of dose absorbed.
[b] Elimination rate constant.
[c] Elimination half-life.
[d] Calculated from one dialysis exchange.
[e] Data from this subject were excluded from the calculated mean values from each kinetic parameter.

present study compares favorably with the values obtained by Singlas et al. (19) in patients undergoing CAPD after being given a 1-g dose intravenously. Also, in both studies, with similar rates of dialysis fluid exchange, comparable values for dialysis clearance of 2.7 ml/min (Singlas et al. [19]), and 2.3 ml/min (present study) were obtained. The percent contribution of CL_D was also comparable in both studies, a value of 17.4 ± 8.9% being obtained by Singlas et al. (19) and 20.0 ± 5.2% in the present study. The agreement in calculated total CL_P between the two studies validates the method of calculation for the fraction of the 1-g dose that is absorbed across the peritoneum.

The apparent V obtained in this study (0.22 ± 0.08 liters/kg) was similar to the value obtained by Singlas et al. (19) (0.21 ± 0.03 liters/kg). Shepherd et al. (18), using a high-pressure liquid chromatography assay for total moxalactam, calculated an apparent V of 0.23 ± 0.05 liters/kg in healthy volunteers. Swanson et al. (20), after studying patients with various degrees of renal failure, found no correlation between the V at steady state and the degree of renal dysfunction. The mean value obtained in healthy volunteers (0.23 liter/kg) compared favorably with that obtained by Shepherd et al. (18) (0.21 liter/kg) after intravenous dosage under steady-state conditions. A V of this magnitude is consistent with distribution mostly into the extracellular fluid. Moxalactam is not highly bound to plasma proteins (25), and thus it would be expected that, despite an approximate 33% increase in the plasma-free fraction during renal failure (17), a less-than-proportionate increase in the V would occur (16).

Data from one subject, patient 8, were comparable with those from other subjects with respect to CL_D, V, and the fraction of the dose absorbed. However, the calculated total CL_P was considerably smaller, and the half-life was greater, than the values obtained for the other seven subjects. Nondialysis clearance was 11% of the total clearance, compared with 80.0% in the other five anuric patients. Other reports of half-lives greater than 30 h associated with total CL_P values of approximately 5 ml/min or less have appeared (9). Diminished liver function, as indicated by chronically elevated concentrations of gamma glutamyltransferase in serum, may offer an explanation for the reduced nondialysis clearance in patient 8.

Poor vascular access in CAPD patients may be the result of fistulae in one or both arms from previous hemodialysis. Since intravenous administration may be more difficult in such patients, an alternative method of drug administration via the peritoneal route is useful. The pharmacokinetic parameters calculated in this study are in agreement with those reported by Singlas et al. (19) after intravenous administration. Similarly, no substantial difference in pharmacokinetics between the intravenous and intraperitoneal route of administration has been observed for cefoperazone (10), cephalexin (4), tobramycin (5), and vancomycin (6). Hence, intraperitoneal administration would be convenient in CAPD patients infected with a microorganism for which moxalactam is indicated. The CL_P determined in the present study is 10 to 15% of the CL_P reported for normal subjects (18). Assuming that 60% of the dose is absorbed after a 4-h dwell time, then the suggested intraperitoneal dose regimen is 1 g initially, which is allowed to dwell in the peritoneal cavity for at least 4 h, followed by 15 to 25% of the recommended dose for normal patients (0.5 to 2 g intravenously every 8 to 12 h for less severe infections [1]) given at the same time intervals, or 30 to 50% of the recommended dose at twice the normal time intervals.

During this study, concentrations of moxalactam in dialysis fluid in the peritoneal cavity well in excess of the reported MIC for the most common pathogen, *Staphylococcus epidermidis* (8, 21), as well as other, less common pathogens, were maintained for the dwell time of the initial dialysis solution containing moxalactam. Because of its broad spectrum of antibiotic activity, moxalactam may be useful in the initial treatment of suspected peritonitis in a CAPD patient who does not have immediate access to antibiotic treatment directed at the causative organism. One or two successive 1-g doses of moxalactam could be given intraperitoneally and allowed to dwell for approximately 4 h, during the time between the development of the symptoms of peritonitis and identification of the pathogen. However, it is unlikely that moxalactam will be the agent of choice once microbiological identification is made, since other antibiotics which are more effective against the microorganisms usually isolated from the dialysate are recommended (23).

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LITERATURE CITED

1. **Aronoff, G. R., R. S. Sloan, and F. C. Luft.** 1982. Pharmacokinetics of moxalactam in patients with normal and impaired renal function. J. Infect. Dis. **145**:365–369.
2. **Aronoff, G. R., R. S. Sloan, S. A. Mong, F. C. Luft, and S. A.**

Kleit. 1981. Moxalactam pharmacokinetics during hemodialysis. Antimicrob. Agents Chemother. **19**:575–577.
3. **Bolton, W. K., W. M. Scheld, D. A. Spyker, T. L. Overby, and M. A. Sande.** 1980. Pharmacokinetics of moxalactam in subjects with various degrees of renal function. Antimicrob. Agents Chemother. **18**:933–938.
4. **Bunke, C. M., G. R. Aronoff, M. E. Brier, R. S. Sloan, and F. C. Luft.** 1983. Cefazolin and cephalexin kinetics during continuous ambulatory peritoneal dialysis. Clin. Pharmacol. Ther. **33**:66–72.
5. **Bunke, C. M., G. R. Aronoff, M. E. Brier, R. S. Sloan, and F. C. Luft.** 1983. Tobramycin kinetics during continuous ambulatory peritoneal dialysis. Clin. Pharmacol. Ther. **34**:110–116.
6. **Bunke, C. M., G. R. Aronoff, M. E. Brier, R. S. Sloan, and F. C. Luft.** 1983. Vancomycin kinetics during continuous ambulatory peritoneal dialysis. Clin. Pharmacol. Ther. **34**:631–637.
7. **Diven, W. F., B. D. Obermeyer, R. L. Wolen, V. L. Yu, J. Lyon, and J. Zuravleff.** 1981. Measurement of serum and tissue concentration of moxalactam using high pressure liquid chromatography. Ther. Drug Monit. **3**:291–295.
8. **Fass, R. J.** 1979. In vitro activity of LY127935. Antimicrob. Agents Chemother. **16**:503–509.
9. **Jacobson, E. J., J. J. Zahrowski, and A. R. Nissenson.** 1981. Moxalactam kinetics in haemodialysis. Clin. Pharmacol. Ther. **30**:487–490.
10. **Keller, E., A. Jansen, K. Pelz, G. Hoppe-Seyler, and P. Scholl-meyer.** 1984. Intraperitoneal and intravenous cefoperazone kinetics during continuous ambulatory peritoneal dialysis. Clin. Pharmacol. Ther. **35**:208–213.
11. **Konaka, R., K. Kuruma, R. Nishimura, Y. Kimura, and T. Yoshida.** 1981. High performance liquid chromatographic analysis of a new β-lactam antibiotic, 6059-S (moxalactam). J. Chromatogr. **225**:169–178.
12. **Leroy, A., G. Humbert, and J. P. Fillastre.** 1981. Pharmacokinetics of moxalactam in subjects with normal and impaired renal function. Antimicrob. Agents Chemother. **19**:965–971.
13. **Lüthy, R., J. Blaser, A. Bonetti, H. Simmen, R. Wise, and W. Siegenthaler.** 1981. Comparative multiple-dose pharmacokinetics of cefotaxime, moxalactam and ceftazidime. Antimicrob. Agents Chemother. **20**:567–575.
14. **Martinez, O. V., J. U. Levi, A. Livingstone, T. I. Malinin, R. Zeppa, D. Hutson, and N. Einhorn.** 1981. Biliary excretion of moxalactam. Antimicrob. Agents Chemother. **20**:231–234.
15. **Nonoshita, Y., M. Yoshida, and M. Menjo.** 1980. Concentration in serum, bile and gallbladder tissue and clinical effect of 6059-S. Chemotherapy (Tokyo) **28**:627–635.
16. **Oie, S., and T. N. Tozer.** 1979. Effect of altered plasma protein binding on apparent volume of distribution. J. Pharm. Sci. **68**:1203–1205.
17. **Petersen, L. R., B. Bean, C. E. Fasching, W. P. Korchik, and D. N. Gerding.** 1981. Pharmacokinetics, protein binding, and predicted extravascular distribution of moxalactam in normal and renal failure subjects. Antimicrob. Agents Chemother. **20**:378–381.
18. **Shepherd, A. M. M., T. C. Hardin, T. M. Ludden, D. J. Miner, and D. L. Coleman.** 1983. Moxalactam kinetics in volunteers studied by a specific HPLC assay technique. J. Antimicrob. Chemother. **12**:377–386.
19. **Singlas, E., H. F. Boutron, H. Merdjan, J. F. Brocard, M. Pocheville, and D. Fries.** 1983. Moxalactam kinetics during chronic ambulatory peritoneal dialysis. Clin. Pharmacol. Ther. **34**:403–407.
20. **Swanson, D. J., D. P. Reitberg, I. L. Smith, P. B. Wels, and J. J. Schentag.** 1983. Steady-state moxalactam pharmacokinetics in patients: non-compartmental versus two-compartmental analysis. J. Pharmacokin. Biopharm. **11**:337–353.
21. **Trager, G. M., G. W. White, V. M. Zimelis, and A. P. Panwalker.** 1979. LY-127935: a novel beta-lactam antibiotic with unusual antibacterial activity. Antimicrob. Agents Chemother. **16**:297–300.
22. **Vas, S. I., D. E. Low, and D. G. Oreopoulos.** 1981. Peritonitis, p. 344–365. *In* K. D. Nolph (ed.), Peritoneal dialysis, Martinus Nijhoff, The Hague.
23. **Williams, P., R. Khanna, S. Vas, S. Layne, D. Pantalony, and D. G. Oreopoulos.** 1980. The treatment of peritonitis in patients on CAPD: to lavage or not? Peritoneal Dialysis Bull. **1**:14–17.
24. **Wright, N., P. J. Wills, and R. Wise.** 1981. The pharmacokinetics of moxalactam in renal failure. J. Antimicrob. Chemother. **8**:395–399.
25. **Yamada, H., T. Ichihashi, K. Hirano, and H. Knowshita.** 1981. Plasma protein binding and urinary excretion of R- and S-epimers of an arylmalonylamino-1-oxacepham in humans. J. Pharm. Sci. **70**:112–113.
26. **Ziemniak, J. A., D. A. Chiarmonte, D. J. Miner, and J. J. Schentag.** 1982. HPLC determination of D and L moxalactam in human serum and urine. J. Pharm. Sci. **71**:399–402.